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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61L 29/00, 31/00

A1

(11) International Publication Number: WO 96/22114

(43) International Publication Date: 25 July 1996 (25.07.96)

(21) International Application Number: PCT/US96/00842

(22) International Filing Date: 18 January 1996 (18.01.96)

(30) Priority Data:
08/374,290 18 January 1995 (18.01.95) US

(71) Applicant: VITAPHORE CORPORATION [US/US]; 1505 O'Brien Drive, Menlo Park, CA 94025 (US).

(72) Inventors: PACETTI, Stephen, D.; 110 E. Remington Drive, No. 35, Sunnyvale, CA 94087 (US). BOND, Emmett, L.; 175 Evandale Avenue, No. 12, Mountain View, CA 94043 (US). JUNGHERR, Lisa, B.; 1348 Country Club Drive, Los Altos, CA 94024 (US).

(74) Agent: SUYAT, Reginald, J.; Fish & Richardson P.C., Suite 100, 2200 Sand Hill Road, Menlo Park, CA 94025 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: AN ANTIMICROBIAL MEDICAL DEVICE AND METHOD

(57) Abstract

The invention relates to an antimicrobial device made using polyurethane and antimicrobial agent, triclosan or a combination of triclosan with a biguanide or silver compound, that provides for a controlled release of the agent. The triclosan has the property of acting as a plasticizer in the polyurethane and being soluble therein.

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AN ANTIMICROBIAL MEDICAL DEVICE AND METHOD

BACKGROUND OF THE INVENTION

The present invention relates generally to a medical device, and more particularly to an antimicrobial medical device made from a polymeric material with an antimicrobial drug incorporated within the polymeric matrix, as well as a method for making such a device.

Many medical devices are made from polymeric materials due to their mechanical properties and/or biocompatibility. Examples of such medical devices include CSF shunts, vascular grafts, endotracheal tubes, peritoneal and hemodialysis tubes, Foley catheters, and percutaneous catheters of all types. However, a major medical complication associated with the use of indwelling medical devices is infection.

For catheters, the infection problem is well documented because catheters are so commonly used. Of the over 40 million patients hospitalized each year, over one-half will have a catheter used as part of their medical procedure. Percutaneously and surgically inserted central venous catheters (CVCs) are used for the administration of fluids, drugs, total parenteral nutrition, and for hemodynamic monitoring. The use of percutaneous catheters disrupt the body's primary barrier to infection, which is the intact skin surface. The wound tract created by catheter placement provides a direct route

for the invasion of microorganisms that cause infections. These infections are typically caused by microorganisms colonizing the surface of the skin.

Coagulase-negative staphylococci (CNS) is the most common cause of vascular access infections. CNS reside as predominant members of the normal skin flora and possess the ability to adhere to and colonize indwelling medical devices. CNS are spherical, gram-positive organisms which cause a variety of diseases in man. Because CNS frequently become drug-resistant, they have risen to a position of special significance in clinical medicine. CNS are uniquely adaptive in exploiting the microenvironment of a percutaneous foreign body. Once established, removal of the device is often necessary to resolve the infection caused by these organisms.

Most CVCs are percutaneously placed acute catheters that have an estimated duration of about one week. The most frequent life-threatening complication from the use of CVCs is septicemia. Even though the use is relatively short term, a CVC-related sepsis rate of 4% is typical. Such infections can prolong hospitalization by an average of 7 days. Unfortunately, CVC-sepsis also has a 10-20% fatality rate.

In the case of a surgically implanted Hickman-type catheter, the mean duration is approximately 3 to 4 months. As a result, infection is a constant threat because the presence of a foreign body will, for a variety of reasons, compromise the normal immune mechanisms of the host against infection. For an immunocompromised patient, especially those on chemotherapy, an infection may result in the discontinuation of therapy, rehospitalization and possibly additional surgery to remove the implant, not to mention the costs and

risks associated therewith. Therefore, prevention of such infections is preferable to treatment, especially when associated with medical devices that are instrumental for patient care.

Many different approaches have been tried to reduce catheter related infection problems. Since these infections are most often associated with bacteria colonizing the catheter surface and forming a biofilm, many schemes have focused on preventing this from occurring. One approach is to reduce the adherence of bacteria to the catheter surface by changing its surface properties. Coating with hydrogels to make the surface more hydrophilic is effective for short periods. However, the main drawback to this approach is that the surfaces of the intravascular device will become conditioned by proteins in the blood, and many microorganisms have the ability to adhere to polymers and proteins.

A second approach involves the use of antimicrobial agent delivered from the polymer. This can be done with a compound that diffuses from the device surface. Different techniques are available to make a catheter into a controlled drug delivery device. The use of a coating containing the drug of interest is well known. The advantage of a coating is that it can be applied to a finished device to add the desired antimicrobial feature. However, there are disadvantages, including limitations in the size of the drug reservoir. There is a practical upper limit of about 100 microns on the coating thickness that can be easily applied. Many commercially available devices have coatings that are only 10 microns thick.

Due to the propensity of CNS to colonize the surfaces of medical devices, any strategy to prevent infection by incorporating an antimicrobial agent into polymers must first address the efficacy against

CNS. The drug 2,4,4'-trichloro-2'-hydroxy diphenyl ether, commonly known as triclosan, is a synthetic antimicrobial agent that is commonly used as an adjunct in cosmetics, soaps and dermatological formulations. It also has limited water solubility, about 10-20 ppm.

Triclosan has a broad antimicrobial spectrum at low concentration and, is active against both gram-positive and gram-negative bacteria, yeast and other fungi. Also, this agent demonstrates a low toxicity and superior activity against CNS.

The approach taken herein is to incorporate an antimicrobial agent in the polymeric material used to make medical devices. However, it is often difficult to obtain the necessary physical characteristics in the polymeric material when combining the antimicrobial agent and the polymer.

It is, therefore, an object of the present invention to provide an antimicrobial medical device that incorporates an antimicrobial agent, or combination of agents, to prevent infections.

Another object of the present invention is to provide an antimicrobial medical device that releases an antimicrobial agent in a controlled manner to provide biocidal properties that are safe and long lasting.

Additional objects and advantages of the invention will be set forth in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention.

SUMMARY OF THE INVENTION

The present invention is directed to a medical device made of a polymeric material that combines polyurethane and an antimicrobial agent, or combination of agents, that acts as a plasticizer in

the formation of the polymeric material. The antimicrobial agent is held in the polymeric matrices, so that migration is inhibited, causing the controlled release of the agent.

The present invention also provides a method of making the antimicrobial medical device wherein an antimicrobial agent is incorporated into the device by blending the agent into the polymer resin before or during extrusion.

The preferred antimicrobial agent is triclosan, which is particularly effective against staphylococci. Combinations of triclosan with biguanides or silver compounds can also be used in the present device. In polyurethane, triclosan will provide long lasting protection against colonization by a broad spectrum of microbes.

The controlled delivery of the antimicrobial agent from the polymeric material is apparently achieved by incorporating the triclosan in the polymeric matrices. Triclosan has unexpected physical properties that render it soluble and completely miscible in polyurethane so that it acts as a plasticizer. As a result, the triclosan can have a high loading in the polyurethane without causing a phase separation. Depending on the specific polymer, the triclosan may obviate the need to use a separate plasticizer in the polymeric material. The triclosan will soften the polymer for processing and provide a degree of elasticity in the formed device. Triclosan is effective at killing certain skin flora, which is the source of infection for most percutaneous and indwelling medical devices.

The biguanides that may be used in the present invention in combination with the triclosan include chlorhexidine acetate, chlorhexidine gluconate, chlorhexidine hydrochloride and

chlorhexidine sulfate, as well as other salts of chlorhexidine. The silver compounds that may be used in the present invention in combination with the triclosan include silver acetate, silver benzoate, silver carbonate, silver iodate, silver iodide, silver lactate, silver laurate, silver nitrate, silver oxide, silver palmitate, silver protein, and silver sulfadiazine.

The medical devices made according to the present invention include catheters, stents, shunts, drainage tubes and other percutaneous devices.

According to the present invention, the term "safe and effective amount" means an amount of antimicrobial agent and/or mixture thereof which is capable of retarding or preventing microbial colonization and adherence to the surface of the polymeric materials used herein while causing minimum undesirable side effects when in contact with living tissue. The amount delivered is above the minimum inhibitory concentration of the targeted microorganisms.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a graph of the serial zone transfer data for extruded blended tubing of the present invention and 5% swell loaded tubing.

Figure 2 is a graph of the serial zone transfer data for the explanted samples tubing used in the in-vivo studies.

Figure 3 is a graph of the assay data for the explanted tubing samples used in the in-vivo studies.

DETAILED DESCRIPTION OF THE INVENTION

According to the invention, the simplest method of incorporating the antimicrobial agent, triclosan, is by direct compounding of the drug into the urethane resin before extrusion. It is a low

cost process and the resulting drug reservoir is large. This can be done only because the drug is compatible with the polymeric material. In addition, polyurethane is easily shaped into three-dimensional structures. Once molded, the formed antimicrobial products are dimensionally stable even after repeated exposure to boiling water and moderately high temperatures.

According to the invention, the term "polyurethane" means a thermoplastic polymer produced by the condensation reaction of a polyisocyanate and a hydroxyl-containing material, including ether-based polyurethane, ester-based polyurethane, poly(ether urethane urea), silicone urethane, in particular, aliphatic or aromatic diisocyanates used in various combinations with polyether, aliphatic or aromatic polyester soft segments to make the thermoplastic polyurethane. Soft segments include high molecular weight polyols with glass transition temperatures typically below room temperature. The preferred polyurethanes have soft segment compositions that are polyether-based or are highly aliphatic. Less preferred polyurethanes are those with polyester soft segments.

The polyurethane must be biocompatible, elastomeric and processable, as well as be able to solubilize triclosan. The polymeric material acts as a reservoir for the triclosan and uniform distribution acts to optimize the loading. For example, triclosan can be incorporated in amounts up to 30% by weight in Tecoflex 80A with no phase separation problems. Tecoflex is a registered trademark of Thermedics, Inc. Tecoflex 80A is an 80 Shore A durometer thermoplastic polyether urethane manufactured using an aliphatic diisocyanate and polyether soft segment.

In the polyurethanes of the present invention, the triclosan acts as a plasticizer. Generally, plasticizers are used in processing polymer materials to soften and improve flow during extrusion without causing any significant loss in other physical properties, such as stiffness, elongation set, etc. Plasticizer can also be used to lower the durometer of a polymeric device. However, the typical plasticizer will leach out slowly and can be toxic. The present use of triclosan alleviates this concern.

At over 30% triclosan loading, the polymeric material becomes soft, sticky and unacceptable for forming the medical devices of the present invention. The preferred loading of triclosan is in the range of 0.5 to 15.0 percent by weight. The more preferred loading of triclosan is in the range of 1.0 to 10.0 percent by weight. The most preferred loading of triclosan is in the range of 5.0 to 10.0 percent. The ultimate loading to attain the required physical properties is dependent, in part, on the durometer of the polymer used. The loading of the triclosan in the present invention can be obtained for durometer values from 75 Shore A to 60 Shore D. For a given softness of the drug loaded polymer, the triclosan loading is higher for polyurethanes of greater durometer.

Extrusion requires that the antimicrobial agent have good thermal stability, which is satisfied by triclosan since it exhibits no significant decomposition below 280-290°C. Triclosan has a measurable vapor pressure at higher temperatures. According to the method of the present invention, extrusion of Tecoflex EG-80A resin is typically carried out at about 160-175°C.

As shown by the present invention, due to its chemical properties, the drug delivery

characteristics of triclosan from polyurethane are well suited for antimicrobial devices. Triclosan is very soluble in urethane and can diffuse through the polymeric material. The triclosan is incorporated into the polymeric matrix and is released when the device is used. When a medical device of the present invention is first inserted into the body, the concentration of drug immediately adjacent to the device depends on the initial concentration of the triclosan, the partition coefficient between the polymer and water, the diffusivity of the triclosan in the urethane, and the rate the drug is swept away from the device.

As used herein, the partition coefficient can be set forth by the following equation:

$$\text{partition coefficient} = \frac{\text{wt.\% drug in water}}{\text{wt.\% drug in polyurethane}}$$

As shown by the present invention, 5% triclosan loading in 80A polyurethane has a partition coefficient of less than 1×10^{-4}.

In addition to the rate of diffusion, the drug delivery rate is also limited by the very low solubility of triclosan in water and its very low partition coefficient between water and polyurethane. These factors prevent the drug from reaching a saturated concentration that is, for example, cytotoxic to red blood cells. In measurements taken in a phosphate buffered saline solution, triclosan has saturation concentration of 16 ppm, which is safe and not toxic to red blood cells. However, the delivery rate is such that the concentration of the drug at the polymer surface is above the minimum inhibitory concentration (MIC) of the targeted microbes so as to be effective. The medical devices of the present invention have the resulting advantageous property of a long duration of activity.

There are several alternative methods that can be used for incorporating the antimicrobial agent into the polymeric material. For example, the resin pellets can be "tumble coated" with triclosan; the resin pellets can be compounded with triclosan using a twin screw compounder; the starting ingredients can be pelletized together using a twin screw machine; and the resin pellets can be compounded with the triclosan using an extruder/compounder machine. Compounding the triclosan and extruding in a single process step is preferred, because the resulting material will have a higher durometer. These methods of compounding the antimicrobial agent into the resin result in the triclosan being uniformly distributed and incorporated into the polymeric matrix.

When using the twin screw compounder, the resin pellets, triclosan and other ingredients, such as fillers and pigments, can also be fed into the compounder at a suitable rate. In the compounder, the ingredients are melted, blended and then extruded into strands. The strands may be pelletized and dried prior to further processing. The homogeneous pellets of polymer and triclosan, prepared as described above, may be remelted and molded or extruded into the desired shape of the medical device.

EXAMPLE

Polyurethane tubing was fabricated with triclosan incorporated directly into the polymer using a loading of triclosan of 5.2 ± .4% by weight. Table 1 shows the tubing samples that were produced. The formulation for the tubing was generally the same as for the Tecoflex products available from Strato Medical, except for the addition of the antimicrobial agent. Also, tubing without the triclosan was made for use in tests as a control.

Table 1. Polyurethane Tubing with Triclosan

1.	Tecoflex EG-80A-B20	Blue (293)	single lumen	0.110 x 0.065	5% triclosan
2.	Tecoflex EG-80A-B20	Blue (293)	single lumen	0.110 x 0.065	0% triclosan (control)
3.	Tecoflex EG-85A-B20	Blue (293)	single lumen	0.110 x. 0.065	5% triclosan
4.	Tecoflex EG-85A-B20	Blue (293)	single lumen	0.110 x. 0.065	0% triclosan (control)

All the resins used were 20% by weight of barium sulphate for radiopacity. The triclosan was blended directly into the Tecoflex resin, which was repelletized by a water pelletizer and extruded to form the tubing. The extrusion was performed without any difficulties. The plasticizer effect of the triclosan permitted the extrusion to be performed at lower temperatures, which may offer a manufacturing advantage.

The physical characteristics of tubing made by the present invention were compared with the control tubing made with triclosan and similar commercially available tubing. For example, the surface of the extruded tubing of the present invention was inspected under an optical microscope. It was found that both the exterior and intraluminal surfaces of the tubing of the present invention were smoother than the control samples and commercially available samples of 9 Fr. tubing from Strato Medical. At room temperature, the drug loaded formulations were not sticky and exhibited no blocking behavior. At 40°C, the 80A tubing with drug was softer but did not block. At 60°C, the 85A tubing blocked slightly, but the lumen would spring back open. However, at 60°C, the 80A tubing tended to stay closed when squeezed.

Both the tubing and the compounded pellets used to produce the tubing were assayed for triclosan

content by the UV-vis method. From the results presented in Table 2, it appears that little, if any, triclosan was lost due to the pelletizing and extrusion processes.

Table 2

Sample	% Triclosan (w/w)
EG-80A-B20 pellets + triclosan	5.1 ± 0.1
EG-85A-B20 pellets + triclosan	5.4 ± 0.2
EG-80A-B20 tubing + triclosan	4.9 ± 0.03
EG-85A-B20 tubing + triclosan	5.1 ± 0.1

Serial zone transfer tests were performed with the extruded 80A and 85A tubing. These test results were compared with some tests for "5%" solvent swell loaded tubing, which was prepared as described below. The zone tests are used to measure a "zone of inhibition," which means a region containing a sufficient concentration of antimicrobial agents that growth and reproduction of microorganisms within the zone are halted. The test organism was Staph. epidermidis and blood agar was the media. The test data showed that there was sustained delivery of the triclosan over several days.

Figure 1 contains the data from the serial zone transfer tests, which are plotted as size of the zone versus time. It was discovered that the 85A tubing and the 5% swell loaded tubing had the same zone behavior during the 5 day test period. Zone size is only moderately sensitive to the drug delivery rate.

Rabbit Implantation In-Vivo Studies:

Triclosan that was swell loaded into polyurethane tubing was used for feasibility in-vivo studies, as described below. The zone tests conducted on swell loaded polyurethane tubing showed results that were similar to using the blended ingredients.

Used as a method for mimicking the blending by or before extrusion of the present invention, swell loading is a simple technique which involves soaking the polyurethane article in a solution containing the triclosan, drying it, and then performing a quick rinse. Swell loading, however, yields a non-uniform drug distribution. In addition, a major drawback of swell loading is that some polymer is extracted and other additives, such as extrusion lubricants and stabilizers, can be leached out as well. The direct blending of the triclosan in the present invention does not have these disadvantages.

For these studies, tube samples with nominal values of "5%" and "10%" of triclosan were prepared by swell loading. The 5% swell loaded tubing contained in the range of 5.5 to 6.1% triclosan, by weight, and the 10% swell loaded tubing contained about 13.9% triclosan, by weight.

The swell loaded tubing was cut into 2 cm segments and sterilized. The lumen of the tube sections were left open. Control sets of tubing with no drug were also prepared. The tube samples were implanted intramuscularly in the backs of white New Zealand rabbits. For each point in time when explants were to be taken, samples of six tube segments for each type of loaded tubing and two control tubing were prepared and implanted. Explants were taken at 30, 60 and 90 days.

Upon retrieval, the implant sites were examined macroscopically and all samples were scored as benign. Further histopathology tests on the implant sites confirmed these initial observations.

While rabbit implant studies were not designed to measure long term biostability of materials, nevertheless, the samples tested showed only minor differences between the drug and non-drug loaded samples. The time zero and 90 day explants were inspected and examined under the microscope for surface changes. Prior to implant, after swell loading and sterilization, all sample surfaces appeared fairly glossy. The drug loaded 90 day implants had a dull surface with no gloss. The surface of the control 90 day implant still had some gloss. Photomicrographs were taken at 200 or 500 magnification in reflectance mode with crossed polarizers. All the samples showed a surface with some striations and tiny knobby features. There is no chemical reason why triclosan would have any adverse effect on a polyether urethane. In addition, by way of comparison, the biostability of the Tecoflex material has been studied extensively and has been shown to be acceptable for a wide range of applications.

Zone of inhibition assays were performed using the recovered explanted samples as well. Figure 2 shows the data plotted as zone size versus time. The test organism was Staph. epidermidis in two different types of agar, i.e., MH and blood agars. After 90 days, both the 10% and 5% samples were still active. As clearly shown in Figure 2, the 10% drug samples give bigger zones than the 5% samples. The results showed that the delivery of the triclosan was not controlled only by the aqueous solubility, since the 10% and 5% samples did not have the same size zones, but may also be controlled by

the diffusion rate in the polymeric material. Distribution of the triclosan in the polymeric material will also be a factor in the delivery rate.

In addition, the triclosan content of the explanted samples were assayed by dissolving the polymer in solvent and measuring the triclosan concentration by UV-vis spectrophotometry. The drug concentrations from the explanted samples are listed in Table 3 below.

Table 3

Drug Totals on Explanted Tubing Samples

Percent Drug by Weight

Sample	Days 0	30	60	90
"5%" Tubing	6.1	2.8	0.75	0.19
"10%" Tubing	13.9	5.5	1.62	0.61

As shown in Figure 3, plotting the above data shows an exponential decay. The above tests show that the extruded blended tubing can be expected to perform as intended and to be effective over an extended period of time. Triclosan present in an amount of about 5%, by weight, will be effective for about 45 days against a microorganism with an MIC of about 1 ppm.

The medical devices made from polyurethanes and triclosan in the present invention will provide long lasting protection against infection. The triclosan will be delivered in an amount that is above the minimum inhibitory concentration of the

targeted microorganisms, including CNS, to prevent colonization of the device surface.

Finally, since numerous modifications and changes will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and operation shown and described, and accordingly all suitable modification and equivalents may fall within the scope of the invention.

WHAT IS CLAIMED IS:

1. A medical device comprising a polymeric material containing polyurethane; and an antimicrobial agent that acts as a plasticizer in said polymeric material and is soluble in said polyurethane, wherein said antimicrobial agent is homogeneously incorporated into said polymeric material and is released from said polymeric material in the presence of biological tissue or fluid in an effective amount to prevent microbial colonization on surfaces of said medical device and in the tissue or fluid surrounding said surfaces.

2. The medical device according to Claim 1 wherein said antimicrobial agent comprises triclosan.

3. The medical device according to Claim 1 wherein said antimicrobial agent comprises triclosan and a biguanide or silver compound.

4. The medical device according to Claim 2 wherein said polymeric material has a durometer value in the range of 75 Shore A to 60 Shore D.

5. The medical device according to Claim 4 wherein said triclosan is present in an amount of up to 30 percent by weight of said polymeric material.

6. The medical device according to Claim 2 wherein said triclosan is present in an amount in the range of 0.5 to 15 percent by weight of said polymeric material.

7. The medical device according to Claim 6 wherein said triclosan is present in an amount of about 5 percent by weight and is effective for about

45 days against a microorganism with a minimum inhibitory concentration of about 1 ppm.

8. The medical device according to Claim 7 wherein said triclosan has a partition coefficient of less than $1x10^{-4}$.

9. The medical device according to Claim 6 wherein said triclosan is present in an amount in the range of 5.0 to 10 percent by weight of said polymeric material.

10. The medical device according to Claim 1 wherein said polyurethane comprises an aliphatic diisocyanate and polyether soft segments.

11. The medical device according to Claim 1 where said polyurethane comprises an aromatic diisocyanate and aliphatic soft segments.

12. The medical device according to Claim 1 wherein said polymeric material is formed into a catheter.

13. The medical device according to Claim 1 wherein said polymeric material is formed into a drainage tube.

14. The medical device according to Claim 1 wherein said polymeric material is formed into a stent.

15. The medical device according to Claim 1 wherein said polymeric material is formed into a shunt.

16. A method for making an antimicrobial medical device comprising blending a polyurethane resin and up to 30 percent of triclosan, by weight, to form a polymeric material, whereby said triclosan is releasably incorporated into said polymeric material; and said triclosan being solubilized in said polyurethane as a plasticizer.

17. The method according to Claim 16 wherein said blending comprises extruding said resin and triclosan to make said medical device.

18. The method according to Claim 16 wherein said polyurethane resin is polyether-based.

19. The method according to Claim 16 wherein said polymeric material has a durometer value in the range of 75 Shore A to 60 Shore D.

Figure 1

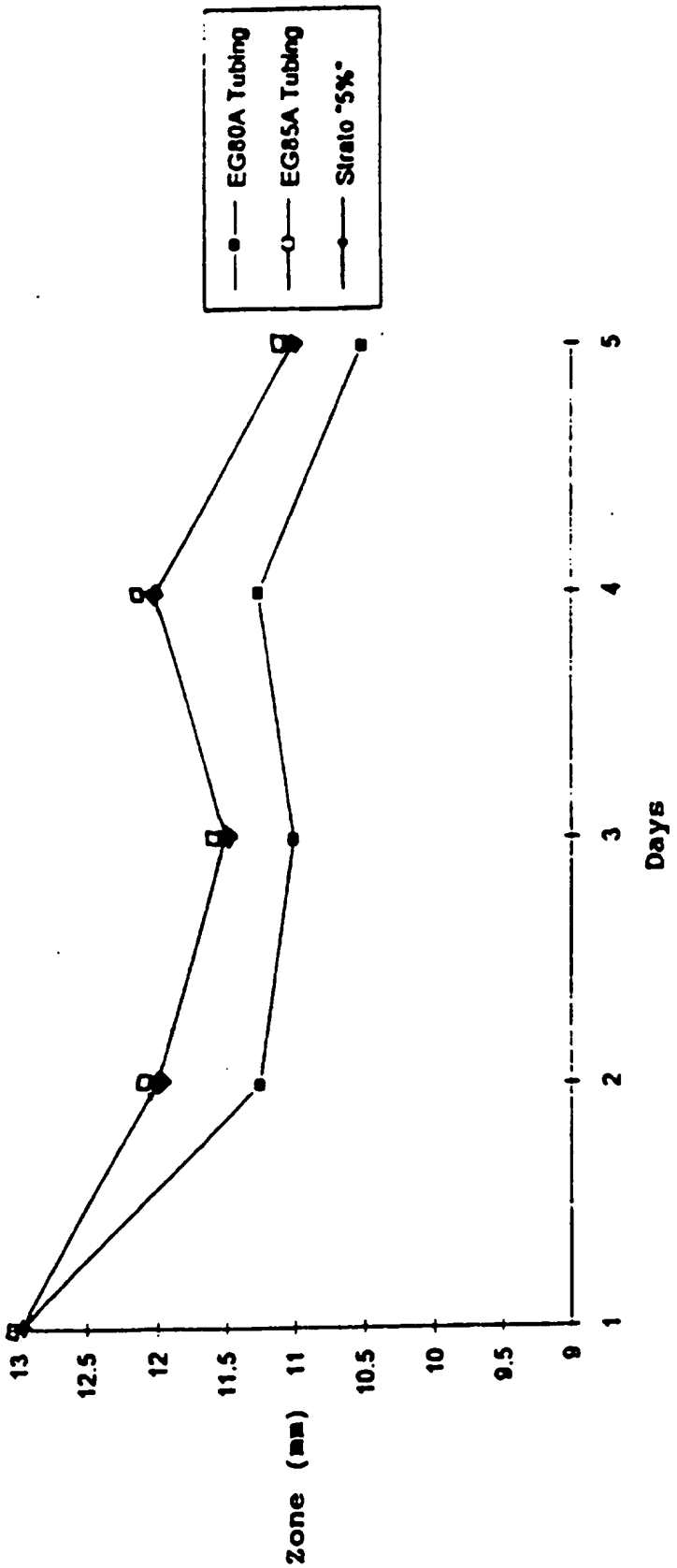
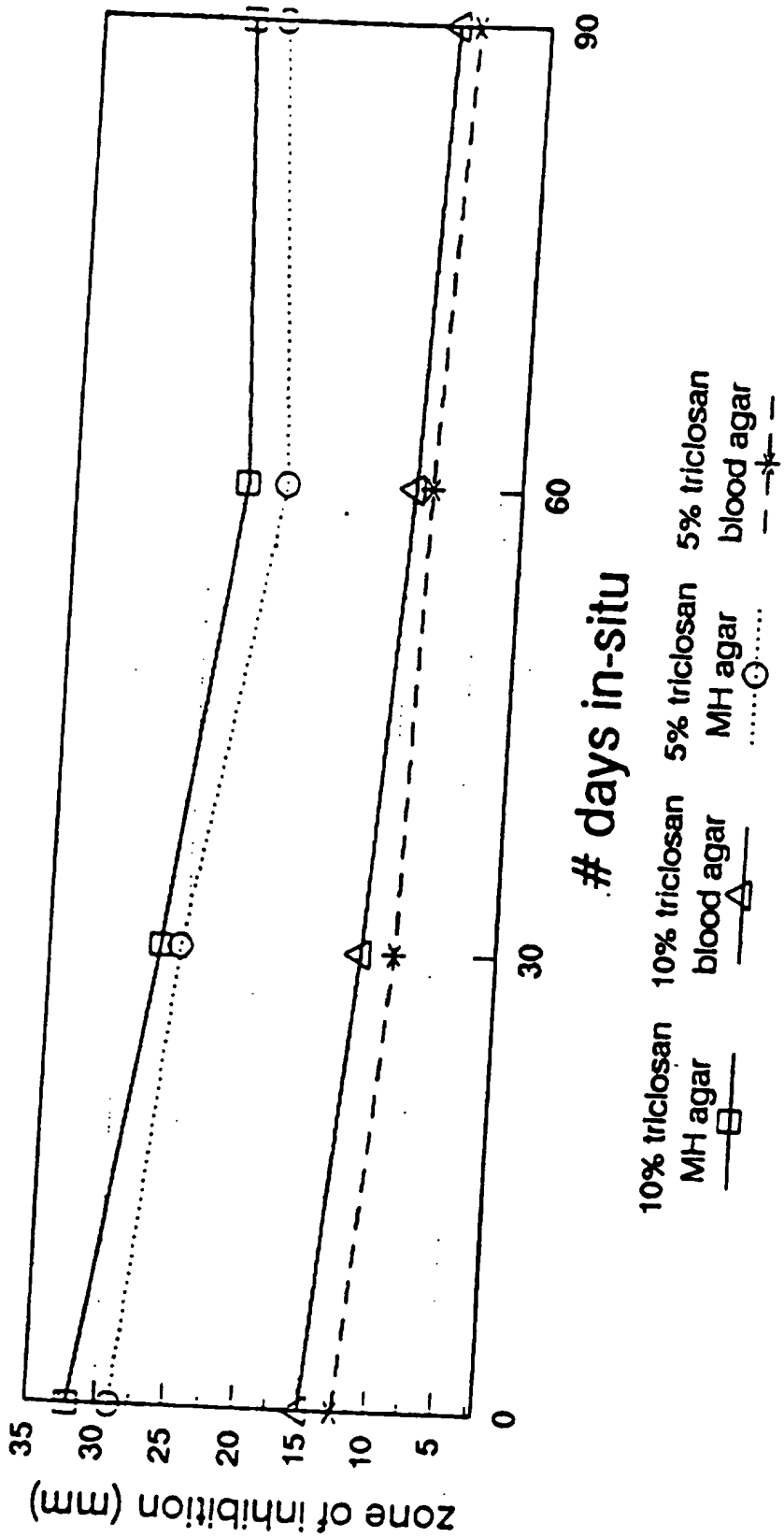

EG80A Tubing
EG85A Tubing
Strato "5%"
Zone (mm)
13
12.5
12
11.5
11
10.5
10
9.5
9
1
2
3
4
5
Days

Figure 2


zone of inhibition (mm)
35
30
25
20
15
10
5
0
30
60
90
days in-situ
10% triclosan MH agar
10% triclosan blood agar
5% triclosan MH agar
5% triclosan blood agar

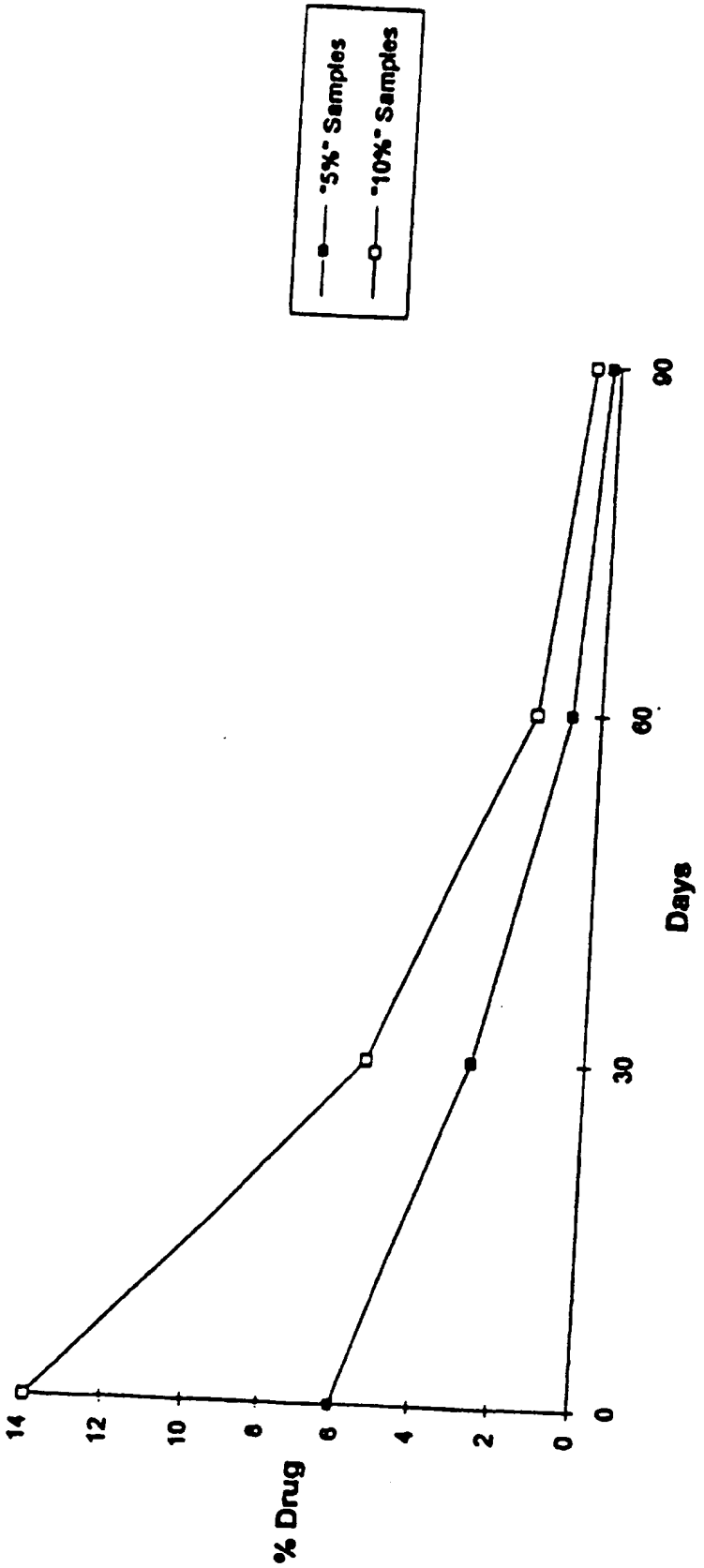


Figure 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/00842

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61L 29/00, 31/00
US CL :424/400, 405, 486; 523/122; 604/264
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/400, 405, 486

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,091,442 A (R. MILNER) 25 February 1992, Abstract, column 1 lines 52-59, column 2 lines 46-51).	1, 2, 6-16, 18, 19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search 04 MAY 1996	Date of mailing of the international search report 15 MAY 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer EDWARD J. WEBMAN Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*

CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61L 29/00, 31/00 — A1

(11) International Publication Number: WO 96/22114

(43) International Publication Date: 25 July 1996 (25.07.96)

(21) International Application Number: PCT/US96/00842

(22) International Filing Date: 18 January 1996 (18.01.96)

(30) Priority Data:
08/374,290 18 January 1995 (18.01.95) US

(71) Applicant: VITAPHORE CORPORATION [US/US]; 1505 O'Brien Drive, Menlo Park, CA 94025 (US).

(72) Inventors: PACETTI, Stephen, D.; 110 E. Remington Drive, No. 35, Sunnyvale, CA 94087 (US). BOND, Emmett, L.; 175 Evandale Avenue, No. 12, Mountain View, CA 94043 (US). JUNGHERR, Lisa, B.; 1348 Country Club Drive, Los Altos, CA 94024 (US).

(74) Agent: SUYAT, Reginald, J.; Fish & Richardson P.C., Suite 100, 2200 Sand Hill Road, Menlo Park, CA 94025 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: AN ANTIMICROBIAL MEDICAL DEVICE AND METHOD

(57) Abstract

The invention relates to an antimicrobial device made using polyurethane and antimicrobial agent, triclosan or a combination of triclosan with a biguanide or silver compound, that provides for a controlled release of the agent. The triclosan has the property of acting as a plasticizer in the polyurethane and being soluble therein.

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AN ANTIMICROBIAL MEDICAL DEVICE AND METHOD

BACKGROUND OF THE INVENTION

The present invention relates generally to a medical device, and more particularly to an antimicrobial medical device made from a polymeric material with an antimicrobial drug incorporated within the polymeric matrix, as well as a method for making such a device.

Many medical devices are made from polymeric materials due to their mechanical properties and/or biocompatibility. Examples of such medical devices include CSF shunts, vascular grafts, endotracheal tubes, peritoneal and hemodialysis tubes, Foley catheters, and percutaneous catheters of all types. However, a major medical complication associated with the use of indwelling medical devices is infection.

For catheters, the infection problem is well documented because catheters are so commonly used. Of the over 40 million patients hospitalized each year, over one-half will have a catheter used as part of their medical procedure. Percutaneously and surgically inserted central venous catheters (CVCs) are used for the administration of fluids, drugs, total parenteral nutrition, and for hemodynamic monitoring. The use of percutaneous catheters disrupt the body's primary barrier to infection, which is the intact skin surface. The wound tract created by catheter placement provides a direct route

for the invasion of microorganisms that cause infections. These infections are typically caused by microorganisms colonizing the surface of the skin.

Coagulase-negative staphylococci (CNS) is the most common cause of vascular access infections. CNS reside as predominant members of the normal skin flora and possess the ability to adhere to and colonize indwelling medical devices. CNS are spherical, gram-positive organisms which cause a variety of diseases in man. Because CNS frequently become drug-resistant, they have risen to a position of special significance in clinical medicine. CNS are uniquely adaptive in exploiting the microenvironment of a percutaneous foreign body. Once established, removal of the device is often necessary to resolve the infection caused by these organisms.

Most CVCs are percutaneously placed acute catheters that have an estimated duration of about one week. The most frequent life-threatening complication from the use of CVCs is septicemia. Even though the use is relatively short term, a CVC-related sepsis rate of 4% is typical. Such infections can prolong hospitalization by an average of 7 days. Unfortunately, CVC-sepsis also has a 10-20% fatality rate.

In the case of a surgically implanted Hickman-type catheter, the mean duration is approximately 3 to 4 months. As a result, infection is a constant threat because the presence of a foreign body will, for a variety of reasons, compromise the normal immune mechanisms of the host against infection. For an immunocompromised patient, especially those on chemotherapy, an infection may result in the discontinuation of therapy, rehospitalization and possibly additional surgery to remove the implant, not to mention the costs and

risks associated therewith. Therefore, prevention of such infections is preferable to treatment, especially when associated with medical devices that are instrumental for patient care.

Many different approaches have been tried to reduce catheter related infection problems. Since these infections are most often associated with bacteria colonizing the catheter surface and forming a biofilm, many schemes have focused on preventing this from occurring. One approach is to reduce the adherence of bacteria to the catheter surface by changing its surface properties. Coating with hydrogels to make the surface more hydrophilic is effective for short periods. However, the main drawback to this approach is that the surfaces of the intravascular device will become conditioned by proteins in the blood, and many microorganisms have the ability to adhere to polymers and proteins.

A second approach involves the use of antimicrobial agent delivered from the polymer. This can be done with a compound that diffuses from the device surface. Different techniques are available to make a catheter into a controlled drug delivery device. The use of a coating containing the drug of interest is well known. The advantage of a coating is that it can be applied to a finished device to add the desired antimicrobial feature. However, there are disadvantages, including limitations in the size of the drug reservoir. There is a practical upper limit of about 100 microns on the coating thickness that can be easily applied. Many commercially available devices have coatings that are only 10 microns thick.

Due to the propensity of CNS to colonize the surfaces of medical devices, any strategy to prevent infection by incorporating an antimicrobial agent into polymers must first address the efficacy against

CNS. The drug 2,4,4'-trichloro-2'-hydroxy diphenyl ether, commonly known as triclosan, is a synthetic antimicrobial agent that is commonly used as an adjunct in cosmetics, soaps and dermatological formulations. It also has limited water solubility, about 10-20 ppm.

Triclosan has a broad antimicrobial spectrum at low concentration and, is active against both gram-positive and gram-negative bacteria, yeast and other fungi. Also, this agent demonstrates a low toxicity and superior activity against CNS.

The approach taken herein is to incorporate an antimicrobial agent in the polymeric material used to make medical devices. However, it is often difficult to obtain the necessary physical characteristics in the polymeric material when combining the antimicrobial agent and the polymer.

It is, therefore, an object of the present invention to provide an antimicrobial medical device that incorporates an antimicrobial agent, or combination of agents, to prevent infections.

Another object of the present invention is to provide an antimicrobial medical device that releases an antimicrobial agent in a controlled manner to provide biocidal properties that are safe and long lasting.

Additional objects and advantages of the invention will be set forth in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention.

SUMMARY OF THE INVENTION

The present invention is directed to a medical device made of a polymeric material that combines polyurethane and an antimicrobial agent, or combination of agents, that acts as a plasticizer in

the formation of the polymeric material. The antimicrobial agent is held in the polymeric matrices, so that migration is inhibited, causing the controlled release of the agent.

The present invention also provides a method of making the antimicrobial medical device wherein an antimicrobial agent is incorporated into the device by blending the agent into the polymer resin before or during extrusion.

The preferred antimicrobial agent is triclosan, which is particularly effective against staphylococci. Combinations of triclosan with biguanides or silver compounds can also be used in the present device. In polyurethane, triclosan will provide long lasting protection against colonization by a broad spectrum of microbes.

The controlled delivery of the antimicrobial agent from the polymeric material is apparently achieved by incorporating the triclosan in the polymeric matrices. Triclosan has unexpected physical properties that render it soluble and completely miscible in polyurethane so that it acts as a plasticizer. As a result, the triclosan can have a high loading in the polyurethane without causing a phase separation. Depending on the specific polymer, the triclosan may obviate the need to use a separate plasticizer in the polymeric material. The triclosan will soften the polymer for processing and provide a degree of elasticity in the formed device. Triclosan is effective at killing certain skin flora, which is the source of infection for most percutaneous and indwelling medical devices.

The biguanides that may be used in the present invention in combination with the triclosan include chlorhexidine acetate, chlorhexidine gluconate, chlorhexidine hydrochloride and

chlorhexidine sulfate, as well as other salts of chlorhexidine. The silver compounds that may be used in the present invention in combination with the triclosan include silver acetate, silver benzoate, silver carbonate, silver iodate, silver iodide, silver lactate, silver laurate, silver nitrate, silver oxide, silver palmitate, silver protein, and silver sulfadiazine.

The medical devices made according to the present invention include catheters, stents, shunts, drainage tubes and other percutaneous devices.

According to the present invention, the term "safe and effective amount" means an amount of antimicrobial agent and/or mixture thereof which is capable of retarding or preventing microbial colonization and adherence to the surface of the polymeric materials used herein while causing minimum undesirable side effects when in contact with living tissue. The amount delivered is above the minimum inhibitory concentration of the targeted microorganisms.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a graph of the serial zone transfer data for extruded blended tubing of the present invention and 5% swell loaded tubing.

Figure 2 is a graph of the serial zone transfer data for the explanted samples tubing used in the in-vivo studies.

Figure 3 is a graph of the assay data for the explanted tubing samples used in the in-vivo studies.

DETAILED DESCRIPTION OF THE INVENTION

According to the invention, the simplest method of incorporating the antimicrobial agent, triclosan, is by direct compounding of the drug into the urethane resin before extrusion. It is a low

cost process and the resulting drug reservoir is large. This can be done only because the drug is compatible with the polymeric material. In addition, polyurethane is easily shaped into three-dimensional structures. Once molded, the formed antimicrobial products are dimensionally stable even after repeated exposure to boiling water and moderately high temperatures.

According to the invention, the term "polyurethane" means a thermoplastic polymer produced by the condensation reaction of a polyisocyanate and a hydroxyl-containing material, including ether-based polyurethane, ester-based polyurethane, poly(ether urethane urea), silicone urethane, in particular, aliphatic or aromatic diisocyanates used in various combinations with polyether, aliphatic or aromatic polyester soft segments to make the thermoplastic polyurethane. Soft segments include high molecular weight polyols with glass transition temperatures typically below room temperature. The preferred polyurethanes have soft segment compositions that are polyether-based or are highly aliphatic. Less preferred polyurethanes are those with polyester soft segments.

The polyurethane must be biocompatible, elastomeric and processable, as well as be able to solubilize triclosan. The polymeric material acts as a reservoir for the triclosan and uniform distribution acts to optimize the loading. For example, triclosan can be incorporated in amounts up to 30% by weight in Tecoflex 80A with no phase separation problems. Tecoflex is a registered trademark of Thermedics, Inc. Tecoflex 80A is an 80 Shore A durometer thermoplastic polyether urethane manufactured using an aliphatic diisocyanate and polyether soft segment.

In the polyurethanes of the present invention, the triclosan acts as a plasticizer. Generally, plasticizers are used in processing polymer materials to soften and improve flow during extrusion without causing any significant loss in other physical properties, such as stiffness, elongation set, etc. Plasticizer can also be used to lower the durometer of a polymeric device. However, the typical plasticizer will leach out slowly and can be toxic. The present use of triclosan alleviates this concern.

At over 30% triclosan loading, the polymeric material becomes soft, sticky and unacceptable for forming the medical devices of the present invention. The preferred loading of triclosan is in the range of 0.5 to 15.0 percent by weight. The more preferred loading of triclosan is in the range of 1.0 to 10.0 percent by weight. The most preferred loading of triclosan is in the range of 5.0 to 10.0 percent. The ultimate loading to attain the required physical properties is dependent, in part, on the durometer of the polymer used. The loading of the triclosan in the present invention can be obtained for durometer values from 75 Shore A to 60 Shore D. For a given softness of the drug loaded polymer, the triclosan loading is higher for polyurethanes of greater durometer.

Extrusion requires that the antimicrobial agent have good thermal stability, which is satisfied by triclosan since it exhibits no significant decomposition below 280-290°C. Triclosan has a measurable vapor pressure at higher temperatures. According to the method of the present invention, extrusion of Tecoflex EG-80A resin is typically carried out at about 160-175°C.

As shown by the present invention, due to its chemical properties, the drug delivery

characteristics of triclosan from polyurethane are well suited for antimicrobial devices. Triclosan is very soluble in urethane and can diffuse through the polymeric material. The triclosan is incorporated into the polymeric matrix and is released when the device is used. When a medical device of the present invention is first inserted into the body, the concentration of drug immediately adjacent to the device depends on the initial concentration of the triclosan, the partition coefficient between the polymer and water, the diffusivity of the triclosan in the urethane, and the rate the drug is swept away from the device.

As used herein, the partition coefficient can be set forth by the following equation:

$$\text{partition coefficient} = \frac{\text{wt.\% drug in water}}{\text{wt.\% drug in polyurethane}}$$

As shown by the present invention, 5% triclosan loading in 80A polyurethane has a partition coefficient of less than $1x10^{-4}$.

In addition to the rate of diffusion, the drug delivery rate is also limited by the very low solubility of triclosan in water and its very low partition coefficient between water and polyurethane. These factors prevent the drug from reaching a saturated concentration that is, for example, cytotoxic to red blood cells. In measurements taken in a phosphate buffered saline solution, triclosan has saturation concentration of 16 ppm, which is safe and not toxic to red blood cells. However, the delivery rate is such that the concentration of the drug at the polymer surface is above the minimum inhibitory concentration (MIC) of the targeted microbes so as to be effective. The medical devices of the present invention have the resulting advantageous property of a long duration of activity.

There are several alternative methods that can be used for incorporating the antimicrobial agent into the polymeric material. For example, the resin pellets can be "tumble coated" with triclosan; the resin pellets can be compounded with triclosan using a twin screw compounder; the starting ingredients can be pelletized together using a twin screw machine; and the resin pellets can be compounded with the triclosan using an extruder/compounder machine. Compounding the triclosan and extruding in a single process step is preferred, because the resulting material will have a higher durometer. These methods of compounding the antimicrobial agent into the resin result in the triclosan being uniformly distributed and incorporated into the polymeric matrix.

When using the twin screw compounder, the resin pellets, triclosan and other ingredients, such as fillers and pigments, can also be fed into the compounder at a suitable rate. In the compounder, the ingredients are melted, blended and then extruded into strands. The strands may be pelletized and dried prior to further processing. The homogeneous pellets of polymer and triclosan, prepared as described above, may be remelted and molded or extruded into the desired shape of the medical device.

EXAMPLE

Polyurethane tubing was fabricated with triclosan incorporated directly into the polymer using a loading of triclosan of 5.2 ± .4% by weight. Table 1 shows the tubing samples that were produced. The formulation for the tubing was generally the same as for the Tecoflex products available from Strato Medical, except for the addition of the antimicrobial agent. Also, tubing without the triclosan was made for use in tests as a control.

Table 1. Polyurethane Tubing with Triclosan

1.	Tecoflex EG-80A-B20	Blue (293)	single lumen	0.110 x 0.065	5% triclosan
2.	Tecoflex EG-80A-B20	Blue (293)	single lumen	0.110 x 0.065	0% triclosan (control)
3.	Tecoflex EG-85A-B20	Blue (293)	single lumen	0.110 x 0.065	5% triclosan
4.	Tecoflex EG-85A-B20	Blue (293)	single lumen	0.110 x 0.065	0% triclosan (control)

All the resins used were 20% by weight of barium sulphate for radiopacity. The triclosan was blended directly into the Tecoflex resin, which was repelletized by a water pelletizer and extruded to form the tubing. The extrusion was performed without any difficulties. The plasticizer effect of the triclosan permitted the extrusion to be performed at lower temperatures, which may offer a manufacturing advantage.

The physical characteristics of tubing made by the present invention were compared with the control tubing made with triclosan and similar commercially available tubing. For example, the surface of the extruded tubing of the present invention was inspected under an optical microscope. It was found that both the exterior and intraluminal surfaces of the tubing of the present invention were smoother than the control samples and commercially available samples of 9 Fr. tubing from Strato Medical. At room temperature, the drug loaded formulations were not sticky and exhibited no blocking behavior. At 40°C, the 80A tubing with drug was softer but did not block. At 60°C, the 85A tubing blocked slightly, but the lumen would spring back open. However, at 60°C, the 80A tubing tended to stay closed when squeezed.

Both the tubing and the compounded pellets used to produce the tubing were assayed for triclosan

content by the UV-vis method. From the results presented in Table 2, it appears that little, if any, triclosan was lost due to the pelletizing and extrusion processes.

Table 2

Sample	% Triclosan (w/w)
EG-80A-B20 pellets + triclosan	5.1 ± 0.1
EG-85A-B20 pellets + triclosan	5.4 ± 0.2
EG-80A-B20 tubing + triclosan	4.9 ± 0.03
EG-85A-B20 tubing + triclosan	5.1 ± 0.1

Serial zone transfer tests were performed with the extruded 80A and 85A tubing. These test results were compared with some tests for "5%" solvent swell loaded tubing, which was prepared as described below. The zone tests are used to measure a "zone of inhibition," which means a region containing a sufficient concentration of antimicrobial agents that growth and reproduction of microorganisms within the zone are halted. The test organism was Staph. epidermidis and blood agar was the media. The test data showed that there was sustained delivery of the triclosan over several days.

Figure 1 contains the data from the serial zone transfer tests, which are plotted as size of the zone versus time. It was discovered that the 85A tubing and the 5% swell loaded tubing had the same zone behavior during the 5 day test period. Zone size is only moderately sensitive to the drug delivery rate.

Rabbit Implantation In-Vivo Studies:

Triclosan that was swell loaded into polyurethane tubing was used for feasibility in-vivo studies, as described below. The zone tests conducted on swell loaded polyurethane tubing showed results that were similar to using the blended ingredients.

Used as a method for mimicking the blending by or before extrusion of the present invention, swell loading is a simple technique which involves soaking the polyurethane article in a solution containing the triclosan, drying it, and then performing a quick rinse. Swell loading, however, yields a non-uniform drug distribution. In addition, a major drawback of swell loading is that some polymer is extracted and other additives, such as extrusion lubricants and stabilizers, can be leached out as well. The direct blending of the triclosan in the present invention does not have these disadvantages.

For these studies, tube samples with nominal values of "5%" and "10%" of triclosan were prepared by swell loading. The 5% swell loaded tubing contained in the range of 5.5 to 6.1% triclosan, by weight, and the 10% swell loaded tubing contained about 13.9% triclosan, by weight.

The swell loaded tubing was cut into 2 cm segments and sterilized. The lumen of the tube sections were left open. Control sets of tubing with no drug were also prepared. The tube samples were implanted intramuscularly in the backs of white New Zealand rabbits. For each point in time when explants were to be taken, samples of six tube segments for each type of loaded tubing and two control tubing were prepared and implanted. Explants were taken at 30, 60 and 90 days.

Upon retrieval, the implant sites were examined macroscopically and all samples were scored as benign. Further histopathology tests on the implant sites confirmed these initial observations.

While rabbit implant studies were not designed to measure long term biostability of materials, nevertheless, the samples tested showed only minor differences between the drug and non-drug loaded samples. The time zero and 90 day explants were inspected and examined under the microscope for surface changes. Prior to implant, after swell loading and sterilization, all sample surfaces appeared fairly glossy. The drug loaded 90 day implants had a dull surface with no gloss. The surface of the control 90 day implant still had some gloss. Photomicrographs were taken at 200 or 500 magnification in reflectance mode with crossed polarizers. All the samples showed a surface with some striations and tiny knobby features. There is no chemical reason why triclosan would have any adverse effect on a polyether urethane. In addition, by way of comparison, the biostability of the Tecoflex material has been studied extensively and has been shown to be acceptable for a wide range of applications.

Zone of inhibition assays were performed using the recovered explanted samples as well. Figure 2 shows the data plotted as zone size versus time. The test organism was Staph. epidermidis in two different types of agar, i.e., MH and blood agars. After 90 days, both the 10% and 5% samples were still active. As clearly shown in Figure 2, the 10% drug samples give bigger zones than the 5% samples. The results showed that the delivery of the triclosan was not controlled only by the aqueous solubility, since the 10% and 5% samples did not have the same size zones, but may also be controlled by

the diffusion rate in the polymeric material. Distribution of the triclosan in the polymeric material will also be a factor in the delivery rate.

In addition, the triclosan content of the explanted samples were assayed by dissolving the polymer in solvent and measuring the triclosan concentration by UV-vis spectrophotometry. The drug concentrations from the explanted samples are listed in Table 3 below.

Table 3

Drug Totals on Explanted Tubing Samples

Percent Drug by Weight

Sample	Days 0	30	60	90
"5%" Tubing	6.1	2.8	0.75	0.19
"10%" Tubing	13.9	5.5	1.62	0.61

As shown in Figure 3, plotting the above data shows an exponential decay. The above tests show that the extruded blended tubing can be expected to perform as intended and to be effective over an extended period of time. Triclosan present in an amount of about 5%, by weight, will be effective for about 45 days against a microorganism with an MIC of about 1 ppm.

The medical devices made from polyurethanes and triclosan in the present invention will provide long lasting protection against infection. The triclosan will be delivered in an amount that is above the minimum inhibitory concentration of the

targeted microorganisms, including CNS, to prevent colonization of the device surface.

Finally, since numerous modifications and changes will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and operation shown and described, and accordingly all suitable modification and equivalents may fall within the scope of the invention.

WHAT IS CLAIMED IS:

1. A medical device comprising a polymeric material containing polyurethane; and an antimicrobial agent that acts as a plasticizer in said polymeric material and is soluble in said polyurethane, wherein said antimicrobial agent is homogeneously incorporated into said polymeric material and is released from said polymeric material in the presence of biological tissue or fluid in an effective amount to prevent microbial colonization on surfaces of said medical device and in the tissue or fluid surrounding said surfaces.

2. The medical device according to Claim 1 wherein said antimicrobial agent comprises triclosan.

3. The medical device according to Claim 1 wherein said antimicrobial agent comprises triclosan and a biguanide or silver compound.

4. The medical device according to Claim 2 wherein said polymeric material has a durometer value in the range of 75 Shore A to 60 Shore D.

5. The medical device according to Claim 4 wherein said triclosan is present in an amount of up to 30 percent by weight of said polymeric material.

6. The medical device according to Claim 2 wherein said triclosan is present in an amount in the range of 0.5 to 15 percent by weight of said polymeric material.

7. The medical device according to Claim 6 wherein said triclosan is present in an amount of about 5 percent by weight and is effective for about

45 days against a microorganism with a minimum inhibitory concentration of about 1 ppm.

8. The medical device according to Claim 7 wherein said triclosan has a partition coefficient of less than $1x10^{-4}$.

9. The medical device according to Claim 6 wherein said triclosan is present in an amount in the range of 5.0 to 10 percent by weight of said polymeric material.

10. The medical device according to Claim 1 wherein said polyurethane comprises an aliphatic diisocyanate and polyether soft segments.

11. The medical device according to Claim 1 where said polyurethane comprises an aromatic diisocyanate and aliphatic soft segments.

12. The medical device according to Claim 1 wherein said polymeric material is formed into a catheter.

13. The medical device according to Claim 1 wherein said polymeric material is formed into a drainage tube.

14. The medical device according to Claim 1 wherein said polymeric material is formed into a stent.

15. The medical device according to Claim 1 wherein said polymeric material is formed into a shunt.

16. A method for making an antimicrobial medical device comprising blending a polyurethane resin and up to 30 percent of triclosan, by weight, to form a polymeric material, whereby said triclosan is releasably incorporated into said polymeric material; and said triclosan being solubilized in said polyurethane as a plasticizer.

17. The method according to Claim 16 wherein said blending comprises extruding said resin and triclosan to make said medical device.

18. The method according to Claim 16 wherein said polyurethane resin is polyether-based.

19. The method according to Claim 16 wherein said polymeric material has a durometer value in the range of 75 Shore A to 60 Shore D.

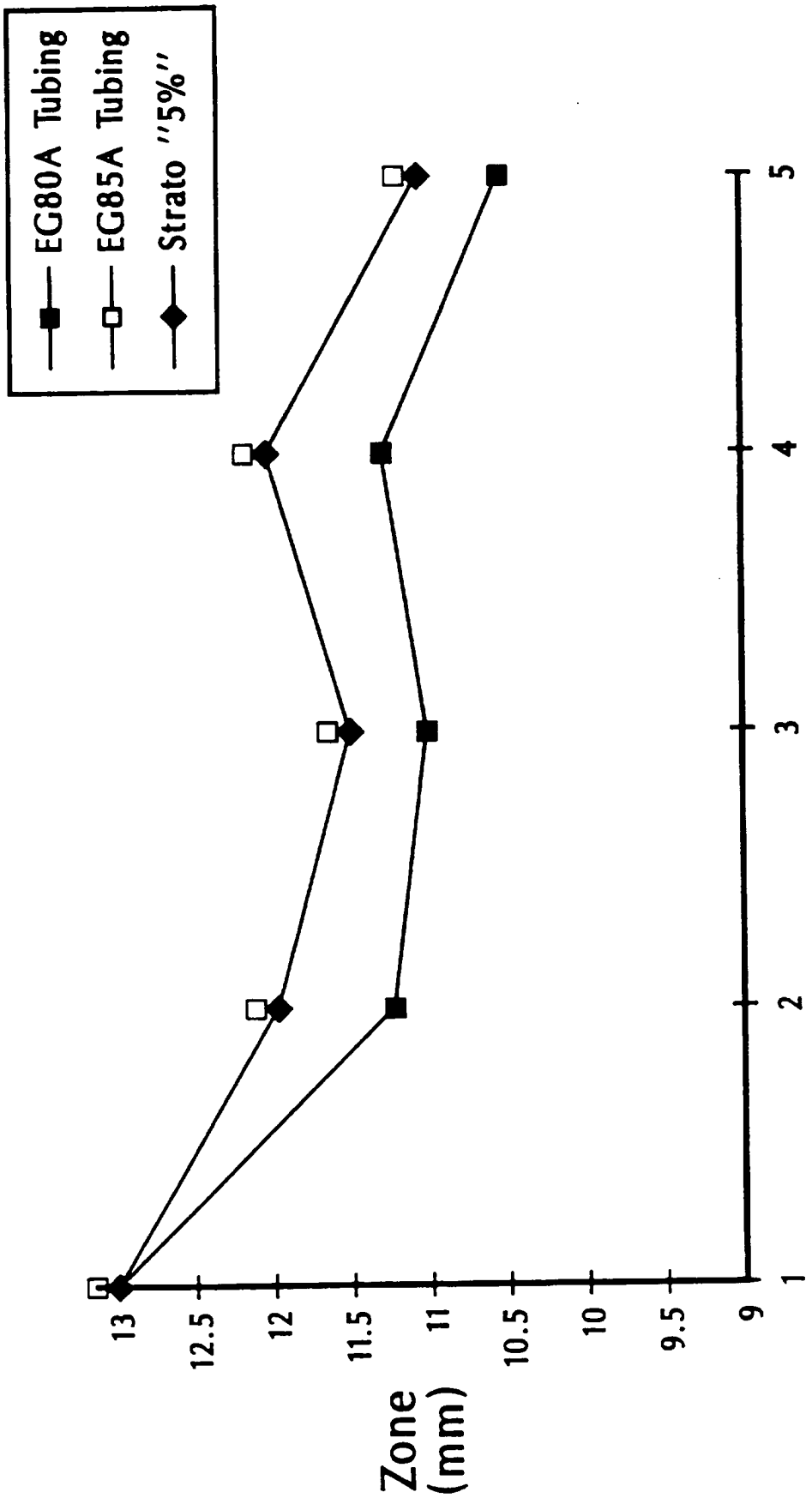
EG80A Tubing
EG85A Tubing
Strato "5%"
Zone (mm)
13
12.5
12
11.5
11
10.5
10
9.5
9
1
2
3
4
5
Days

FIG. 1

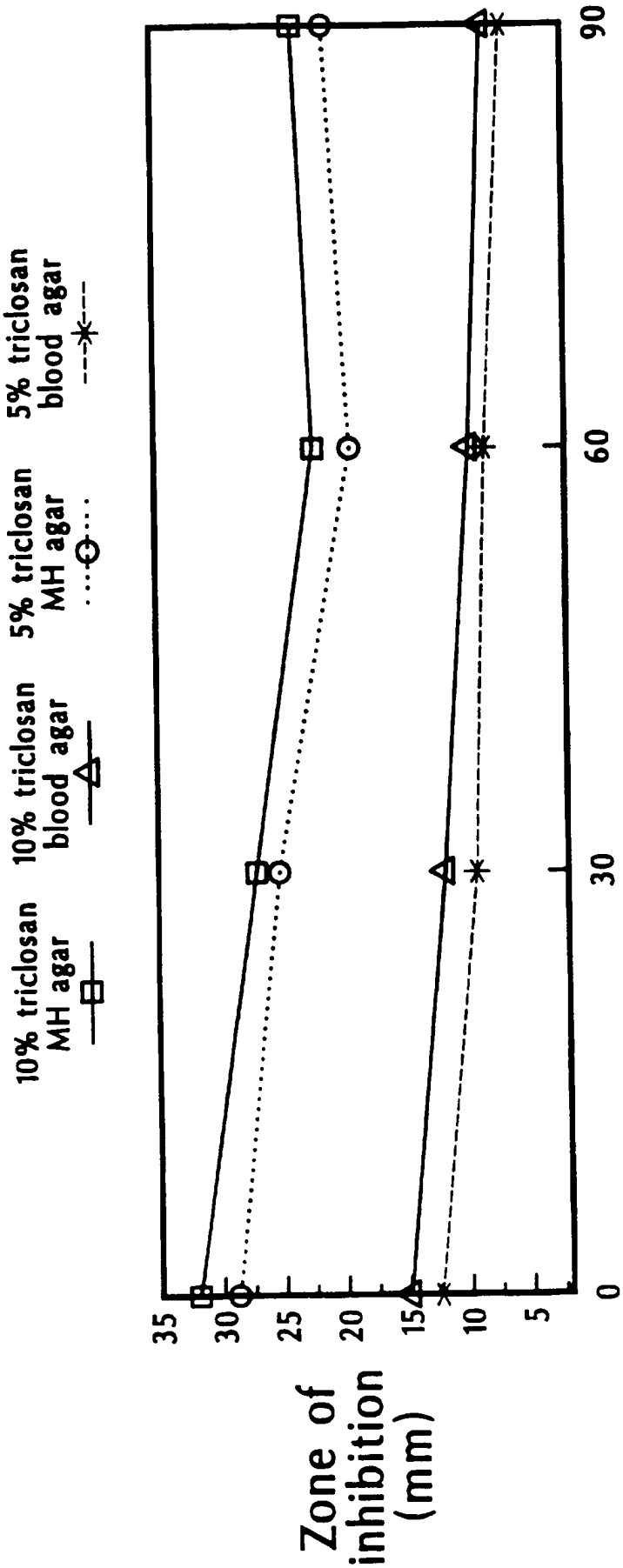
10% triclosan MH agar
10% triclosan blood agar
5% triclosan MH agar
5% triclosan blood agar
Zone of inhibition (mm)
35
30
25
20
15
10
5
0
30
60
90
#Days in-situ

FIG. 2

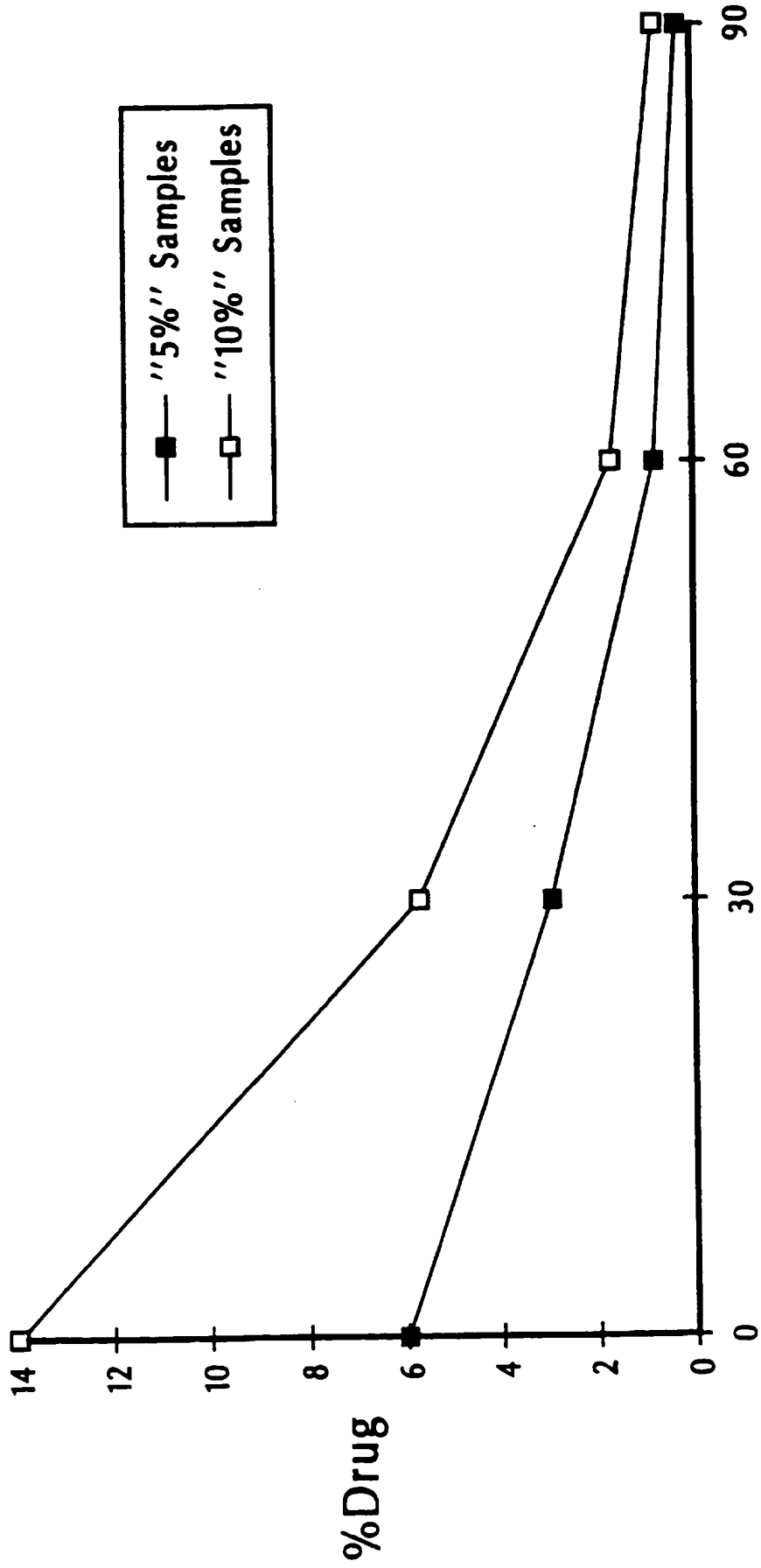

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/00842

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61L 29/00, 31/00
US CL :424/400, 405, 486; 523/122; 604/264
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/400, 405, 486

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,091,442 A (R. MILNER) 25 February 1992, Abstract, column 1 lines 52-59, column 2 lines 46-51).	1, 2, 6-16, 18, 19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
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Date of the actual completion of the international search
04 MAY 1996

Date of mailing of the international search report
15 MAY 1996

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
EDWARD J. WEBMAN
Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*